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EDWARDS & ANGELL, LLP			LI, RUIXIANG	
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Please find below and/or attached an Office communication concerning this application or proceeding.

DETAILED ACTION

Election/Restrictions

1. Applicants' election with traverse of Group I, Claims 1-38 in the reply filed on 02/10/2006 is acknowledged. The traversal is on the ground(s) that (i) the subject matter of the two groups of inventions represents different embodiments of a single inventive concept; and (ii) a sufficient search and examination of the two groups of inventions can be made without serious burden. This has been fully considered but is not found persuasive because (i) an examiner may limit the examination of an application to one of a plurality of patentably distinct inventions under 35 U.S.C. 121, not *a single inventive concept*; and (ii) Group I and Group II, while related as product and process of use, are two distinct inventions and require non-cohesive searches and considerations.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-42 are pending. Claims 1-38 are under consideration and Claims 39-42 are withdrawn from consideration.

Claim Rejections—35 USC §112, 2nd paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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4. Claims 9, 10, and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9 and 10 indefinite because of the term "reporter gene". The correct term appears to be "reporter" in view of the instant disclosure and the claims.

Claim 19 is indefinite because of the term "SPA". It should be spelled out.

Claim Rejections—35 USC §102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6. Claims 1-4, 35, and 38 are rejected under 35 U.S.C. 102(e) as being anticipated by Trueheart et al. (U.S. Patent No: 6159705, December 12, 2000, filed on September 24, 1997). Trueheart et al. teach an assay for identifying a compound that modulates a heterologous receptor that is functionally integrated into an endogenous yeast pheromone response pathway (See, Claims 1 and 2). Trueheart teach that the cells used in the assay can be any type of cells, including yeast cells or MATa *Saccharomyces cerevisiae* cells (Column 2, 4th paragraph; Column 13, line 4;

Column 15, last two paragraphs). Trueheart et al. further teach a G-protein coupled receptor (C5a receptor) functionally coupled to the endogenous yeast GPA-1 protein subunit (Column 61, example 4), meeting the limitations of claims 1-4, 35 and 38.

Claim Rejections—35 USC § 103 (a)

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. Claims 5, 11, 14, 16, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart et al. (U.S. Patent No: 6159705, December 12, 2000, filed on September 24, 1997) in view of Cappellaro et al. (EMBO J. 10 :4081-4088, 1991).

Trueheart et al. teach a method for identifying a compound that modulates a heterologous receptor in a cell, as discussed above. Trueheart et al. fail to teach (1) the use of the protein product of AGA2 gene (a-agglutinin) as a detectable signal (re: claim 5); (2) a detector molecule conjugated with a reporter moiety (re: claims 11 and 14); or (3) an extraction step comprising treatment of the cells with a reducing agent (re: claims 16 and 17).

Cappellaro et al. teach the characterization of AGA2 gene and protein, as well as the interaction of the protein product of AGA2 gene (a-agglutinin) with α -agglutinin (See the whole document). Cappellaro et al. also teach staining of yeast cells to

detect a-agglutinin with an anti-a-agglutinin antibody labelled with FITC (page 4087, last paragraph-page 4088, 1st paragraph). Cappellaro et al. further teach extraction of a-agglutinin from MATa *S. cerevisiae* yeast cells by treating the cells with a reducing agent, dithiothreitol (page 4081, right column, 3rd paragraph).

Therefore, It would have been obvious to one having ordinary skill in the art at the time the invention was made to include (1) the use of the protein product of AGA2 gene (a-agglutinin) as a detectable signal; (2) the use of an anti-a-agglutinin antibody labelled with FITC for the detection of a-agglutinin; or (3) the extraction step comprising treatment of the cells with a reducing agent in the method taught by Trueheart et al. with a reasonable expectation of success. One skilled in the art would have been motivate to do so because (1) activation of pheromone response pathway induces production of the protein product of AGA2 gene (a-agglutinin) that specifically reacts with and binds to α -agglutinin (page 4082, right column, 5th paragraph), (2) treatment of the cells with a reducing agent results in release the cell surface signal molecules (such as a-agglutinin), and (3) an fluorescing antibody offers a sensitive means for the detection of a signal, as taught by Cappellaro et al.

9. Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart et al. (U.S. Patent No: 6159705, December 12, 2000, filed on September 24, 1997) in view of Cappellaro et al. (EMBO J. 10 :4081-4088, 1991), as applied to Claims 5, 11, 14, 16, and 17 above, and further in view of Wojciechowicz et al (Mol. Cell. Biol. 13:2554-2563, 1993).

Trueheart et al. teach a method for identifying a compound that modulates a heterologous receptor in a cell and Cappellaro et al. teach the use of an fluorescing a-agglutinin antibody in the detection of a-agglutinin, as discussed above.

Trueheart et al. and Cappellaro et al. fail to teach the use of Sag1 protein comprising amino acids 20-352 of the mature protein as a detector molecule.

However, Wojciechowicz et al teach that a-Agglutinin consists of two subunits, a core subunit (Aga1), which mediates cell surface attachment, and a binding domain (Aga2), which interacts with and binds to Sag1 protein (α -agglutinin; page 2554, 2nd paragraph). Wojciechowicz et al further teach that the N-terminal (first 350 amino acids of α -agglutinin) contains the binding domain of α -agglutinin (page 2554, right column, 2nd paragraph; page 2559, right column, 3rd paragraph).

Therefore, It would have been obvious to one having ordinary skill in the art at the time the invention was made to include the Sag1 protein or Sag1 protein comprising amino acids 20-352 of the mature protein of Wojciechowicz et al. in the method taught by Trueheart et al. and Cappellaro et al. with a reasonable expectation of success. One skilled in the art would be motivated to do so because the Sag1 protein or Sag1 protein comprising amino acids 20-352 of the mature protein specifically binds to a-Agglutinin.

10. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart et al. (U.S. Patent No: 6159705, December 12, 2000, filed on September 24, 1997) in view of both Cappellaro et al. (EMBO J. 10:4081-4088, 1991) and Wojciechowicz et

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al. (Mol. Cell. Biol. 13:2554-2563, 1993), as applied to claims 12 and 13 above, and further in view of Wu et al. (Analytical Biochemistry, 249:29-36, 1997).

Trueheart et al. teach a method for identifying a compound that modulates a heterologous receptor in a cell, Cappellaro et al. teach staining of yeast cells to detect a-agglutinin with an anti-a-agglutinin antibody labelled with FITC (page 4087, last paragraph-page 4088, 1st paragraph), and Wojciechowicz et al. teach Sag1 protein, as discussed above.

Trueheart et al, Cappellaro et al, and Wojciechowicz et al. fail to teach the use of fluorescence polarization technique.

However, fluorescence polarization technique is well known in the art. It has been used to measure a variety of molecular interactions, including ligand-receptor, protein-protein, and protein-DNA interactions. For example, Wu et al. teach the use of fluorescence polarization in a high-throughput STAT binding assay. Fluorescence polarization has a number of advantages, including (1) the assay is done in homogeneous solution, thus eliminating possible complications arising from solid-phase base assays and the equilibrate time is short which reduces overall assay time; (2) fluorescence polarization is measured in ratio mode, thus avoiding intensity fluctuation; and (3) the technique can be applied to weak binding systems where dissociation is very fast (page 29, right column, last paragraph-page 30, left column, 1st paragraph).

Therefore, It would have been obvious to one having ordinary skill in the art at the time the invention was made to include fluorescence polarization in the method

taught by Trueheart et al, Cappellaro et al, and Wojciechowicz et al. with a reasonable expectation of success. One skilled in the art would have been motivated to do so because fluorescence polarization is a very useful developmental tool for the optimization of measuring binding processes, as taught by Wu et al (page 29, right column, last paragraph-page 30, left column, 1st paragraph).

11. Claims 18-20 and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart et al. (U.S. Patent No: 6159705, December 12, 2000, filed on September 24, 1997) in view of Cappellaro et al. (EMBO J. 10 :4081-4088, 1991), as applied to Claims 5, 11, 14, 16, and 17, and further in view of both Alberts et al. (Molecular Biology of the Cell, 2nd Edition, Garland Publishing, Inc, 1989) and Nare et al. (Analytical Biochemistry, 267:390-396, 1999).

Trueheart et al. teach a method for identifying a compound that modulates a heterologous receptor in a cell and the means of detection of emitted light, including chemiluminescence (Column 70, line 48). Cappellaro et al. teach an extraction step comprising treatment of the cells with a reducing agent, as discussed above. Trueheart et al. and Cappellaro et al. did not teach binding a detectable signal to a support and incubating the support with a detection molecule conjugated with a reporter moiety.

However, use of such technique is well known in the art. For example, Alberts et al. teach the detection of an immobilized antigen using biotin-coupled primary antibody, which specifically binds to the antigen, as well as labeled streptavidin (page 177; page 178, Figure 4-58). Nare et al. teach the use of streptavidin-coated SPA

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beads containing scintillant in a scintillation proximity assay of measuring ^3H radiolabel signal (See, eg, Abstract and Fig. 2).

Therefore, It would have been obvious to one having ordinary skill in the art at the time the invention was made to include the steps taught by Alberts et al. and Nare et al. in the method of Trueheart et al. and Cappellaro et al. with a reasonable expectation of success. The motivation to do so would have been to develop the most sensitive method using the described detection molecule conjugated with a reporter moiety, as taught by Alberts et al. (pages 177-178).

12. Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart et al. (U.S. Patent No: 6159705, December 12, 2000, filed on September 24, 1997) in view of Cappellaro et al. (EMBO J. 10:4081-4088, 1991) and Alberts et al. (Molecular Biology of the Cell, 2nd Edition, Garland Publishing, Inc, 1989) and Nare et al. (Analytical Biochemistry, 267:390-396, 1999), as applied to claims 18-20, 23 and 24 above, and further in view of Wojciechowicz et al (Mol. Cell. Biol. 13:2554-2563, 1993).

Trueheart et al. teach a method for identifying a compound that modulates a heterologous receptor in a cell, Cappellaro et al. teach an extraction step comprising treatment of the cells with a reducing agent; Alberts et al. teach the use of labeled streptavidin, which specifically binds to the biotin-coupled antibody, which, in turn, binds to a detectable signal; and Nare et al teach the use of streptavidin-coated SPA beads containing scintillant in a scintillation proximity assay of measuring ^3H

radiolabel signal. However, all of them fail to teach the use of Sag1 protein comprising amino acids 20-352 of the mature protein as a detector molecule.

Wojciechowicz et al teach that a-Agglutinin consists of two subunits, a core subunit (Aga1), which mediates cell surface attachment, and a binding domain (Aga2), which interacts with and binds to Sag1 protein (α -agglutinin; page 2554, 2nd paragraph). Wojciechowicz et al. further teach that the N-terminal (first 350 amino acids of α -agglutinin) contains the binding domain of α -agglutinin (page 2554, right column, 2nd paragraph; page 2559, right column, 3rd paragraph).

Therefore, It would have been obvious to one having ordinary skill in the art at the time the invention was made to include the Sag1 protein or Sag1 protein comprising amino acids 20-352 of the mature protein of Wojciechowicz et al. in the method taught by Trueheart et al, Cappellaro et al, Alberts et al., and Nare et al. with a reasonable expectation of success. One skilled in the art would be motivated to do so because the Sag1 protein or Sag1 protein comprising amino acids 20-352 of the mature protein specifically binds to a-Agglutinin.

13. Claims 6, 9-11, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart et al. (U.S. Patent No: 6159705, December 12, 2000, filed on September 24, 1997) in view of Alberts et al. (Molecular Biology of the Cell, 2nd Edition, Garland Publishing, Inc, 1989).

Trueheart et al. teach a method for identifying a compound that modulates a heterologous receptor in a cell, as discussed above. Trueheart et al. fail to teach a detector molecule conjugated with a reporter moiety.

However, use of a detector molecule conjugated with a reporter moiety is well known in the art. For example, Alberts et al. teach the use of antibodies coupled with a marker molecule (a reporter) for detecting specific molecules in cells (page 177; page 178, Figure 4-58). Alberts also teach the use of a fluorescent dye and an enzyme (alkaline phosphatase, horseradish peroxidase) (page 177; page 178, Figure 4-58).

Therefore, It would have been obvious to one having ordinary skill in the art at the time the invention was made to include a detector molecule conjugated with a reporter moiety in the method taught by Trueheart et al. with a reasonable expectation of success. The motivation to do so would have been to develop the most sensitive method using an antibody conjugated with a reporter moiety, as taught by Alberts et al. (pages 177-178).

14. Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart et al. (U.S. Patent No: 6159705, December 12, 2000, filed on September 24, 1997) in view of Alberts et al. (Molecular Biology of the Cell, 2nd Edition, Garland Publishing, Inc, 1989) as applied to Claims 6, 9-11 and 14 above, and further in view of Wojciechowicz et al (Mol. Cell. Biol. 13:2554-2563, 1993).

Trueheart et al. teach a method for identifying a compound that modulates a heterologous receptor in a cell and Alberts et al. teach the use of a detectable molecule conjugated with reporter moiety, as discussed above.

Trueheart et al. and Alberts et al. fail to teach the use of Sag1 protein comprising amino acids 20-352 of the mature protein as a detector molecule.

However, Wojciechowicz et al teach that a-Agglutinin consists of two subunits, a core subunit (Aga1), which mediates cell surface attachment, and a binding domain (Aga2), which interacts with and binds to Sag1 protein (α -agglutinin; page 2554, 2nd paragraph). Wojciechowicz et al further teach that the N-terminal (first 350 amino acids of α -agglutinin) contains the binding domain of α -agglutinin (page 2554, right column, 2nd paragraph; page 2559, right column, 3rd paragraph).

Therefore, It would have been obvious to one having ordinary skill in the art at the time the invention was made to include the Sag1 protein or Sag1 protein comprising amino acids 20-352 of the mature protein in the method taught by Trueheart et al. and Alberts et al. with a reasonable expectation of success. One skilled in the art would be motivated to do so because the Sag1 protein or Sag1 protein comprising amino acids 20-352 of the mature protein specifically binds to a-Agglutinin.

15. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart et al. (U.S. Patent No: 6159705, December 12, 2000, filed on September 24, 1997) in view of Roy et al. (Mol. Cell. Biol. 11:4196-4206, 1991).

Trueheart et al. teach a method for identifying a compound that modulates a heterologous receptor in a cell, as discussed above. Trueheart et al. fail to teach *S. cerevisiae* cells with the AGA1 gene deleted.

Roy et al. teach active a-agglutinin binding subunit (AGA2 gene product) is secreted by aga1 mutants (Abstract, lines 12-13; page 4200, right column, 3rd paragraph; page 4203, right column, 3rd paragraph).

Therefore, It would have been obvious to one having ordinary skill in the art at the time the invention was made to include the use of *aga1* mutants in the method taught by Trueheart et al. with a reasonable expectation of success. The motivation to do so would have been in the recognition that such mutants release the cell surface signal molecules (such as α -agglutinin) spontaneously, as taught by Roy et al.

16. Claims 27-29 and 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart et al. (U.S. Patent No: 6159705, December 12, 2000, filed on September 24, 1997) in view of Roy et al. (Mol. Cell. Biol. 11:4196-4206, 1991) as applied to claim 26 above, and further in view of both Alberts et al. (Molecular Biology of the Cell, 2nd Edition, Garland Publishing, Inc, 1989) and Nare et al. (Analytical Biochemistry, 267:390-396, 1999).

Trueheart et al. teach a method for identifying a compound that modulates a heterologous receptor in a cell and the means of detection of emitted light, including chemiluminescence (Column 70, line 48). Roy et al. teach active α -agglutinin binding subunit (AGA2 gene product) is secreted by *aga1* mutants as discussed above. Neither Trueheart et al. nor Roy et al. teach binding the secreted AGA2 gene product to a support and incubating the support with a detection molecule conjugated with a reporter moiety.

However, use of such technique is well known in the art. For example, Alberts et al. teach the detection of an immobilized antigen using biotin-coupled primary antibody, which specifically binds to the antigen, as well as labeled streptavidin (page

177; page 178, Figure 4-58). Nare et al. teach the use of streptavidin-coated SPA beads containing scintillant in a scintillation proximity assay of measuring ^3H radiolabel signal (See, eg, Abstract and Fig. 2).

Therefore, It would have been obvious to one having ordinary skill in the art at the time the invention was made to include the steps taught by Alberts et al. and Nare et al. in the method of Trueheart et al. and Roy et al. with a reasonable expectation of success. The motivation to do so would have been to develop the most sensitive method using the described detection molecule conjugated with a reporter moiety, as taught by Alberts et al. (pages 177-178).

17. Claims 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart et al. (U.S. Patent No: 6159705, December 12, 2000, filed on September 24, 1997) in view of both Roy et al. (Mol. Cell. Biol. 11:4196-4206, 1991), Alberts et al. (Molecular Biology of the Cell, 2nd Edition, Garland Publishing, Inc, 1989), and Nare et al. (Analytical Biochemistry, 267:390-396, 1999), as applied to claims 27-29, 32, and 33, and further in view of Wojciechowicz et al (Mol. Cell. Biol. 13:2554-2563, 1993).

Trueheart et al. teach a method for identifying a compound that modulates a heterologous receptor in a cell; Roy et al teach active a-agglutinin binding subunit (AGA2 gene product) is secreted by aga1 mutants; Alberts et al. teach the use of labeled streptavidin, which specifically binds to the biotin-coupled antibody, which, in turn, binds to a detectable signal, as discussed above; and Nare et al. teach the use of streptavidin-coated SPA beads containing scintillant in a scintillation proximity

assay of measuring ^3H radiolabel signal. However, all of them fail to teach the use of Sag1 protein comprising amino acids 20-352 of the mature protein as a detector molecule.

Wojciechowicz et al teach that a-Agglutinin consists of two subunits, a core subunit (Aga1), which mediates cell surface attachment, and a binding domain (Aga2), which interacts with and binds to Sag1 protein (α -agglutinin; page 2554, 2nd paragraph). Wojciechowicz et al further teach that the N-terminal (first 350 amino acids of α -agglutinin) contains the binding domain of α -agglutinin (page 2554, right column, 2nd paragraph; page 2559, right column, 3rd paragraph).

Therefore, It would have been obvious to one having ordinary skill in the art at the time the invention was made to include the Sag1 protein or Sag1 protein comprising amino acids 20-352 of the mature protein of Wojciechowicz et al. in the method taught by Trueheart et al, Roy et al, Alberts et al. and Nare et al with a reasonable expectation of success. One skilled in the art would be motivated to do so because the Sag1 protein or Sag1 protein comprising amino acids 20-352 of the mature protein specifically binds to a-Agglutinin.

18. Claims 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart et al. (U.S. Patent No: 6159705, December 12, 2000, filed on September 24, 1997) in view of Reppert (U.S. Patent No. 6037,131, March 14, 2000, filed on March 29, 1999).

Trueheart et al. teach a method for identifying a compound that modulates a heterologous receptor in a cell. Trueheart et al. fail to teach the use of melatonin 1a receptor and other heterologous receptors listed in claim 36.

However, all the receptors listed in claim 36 have been cloned and well characterized. For example, Reppert teaches expression of melatonin 1a receptor gene in mammalian cells (Column 7, Example 2).

Therefore, It would have been obvious to one having ordinary skill in the art at the time the invention was made to include melatonin 1a receptor of Reppert in the method taught by Trueheart et al. with a reasonable expectation of success. One skilled in the art would be motivated to do so because melatonin 1a receptor has important biological functions.

Claim Objections

19. Claims 36 and 37 are objected to as being dependent upon a rejected claim.

Conclusion

20. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's

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supervisor, Brenda Brumback, can be reached on (571) 272-0961. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

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